Atopic Dermatitis

Mark Boguniewicz, MD
Professor, Division of Allergy-Immunology
Department of Pediatrics
National Jewish Medical and Research Center
and University of Colorado School of Medicine

Disclosures

- Research grants
  - Novartis, Sinclair
- Lecture honoraria
  - Novartis, Astellas
- Consulting
  - Graceway

Introduction

- Atopic dermatitis is the most common chronic skin disease of young children, but can affect patients of any age
- Prevalence of AD (> 10%) has continued to increase similarly to respiratory allergies/asthma
- Questionnaire study of an ethnically diverse population of Oregon children ages 5-9 years born 1987-1991 showed lifetime prevalence to be ~17%

Laughter D, et al. J Am Acad Dermatol 2000;43:649

Atopic dermatitis and QOL

- AD is an important cause of school absenteeism and occupational disability and impacts significantly on patient/family QOL
- Sleep disruption is a major problem for patients and families (~2.6 h/night)
- Often persists even with disease in remission

Chamlin S, et al. Arch Pediatr Adolesc Med 2005;159:745

Atopic march

- Over 50% of patients with AD will develop asthma and a higher percentage will develop allergies
- Increased numbers of IgE(+) LCs in both active AD & asthma vs inactive AD or asthma, suggesting systemic regulation of active allergic disease, further aggravated by local inflammation in atopic skin lesions

Semper AE et al. J Allergy Clin Immunol 2003;112:411

Natural history

- AD typically presents in early childhood with onset before five years of age in approximately 90% of patients
- In adults with new onset dermatitis, especially without a history of childhood eczema, asthma or allergic rhinitis, other diseases need to be considered

Differential diagnosis of AD

Congenital disorders
- Netherton's syndrome

Chronic dermatoses
- Seborrheic dermatitis
- Contact dermatitis (allergic or irritant)
- Nummular eczema
- Lichen simplex chronicus

Infections and infestations
- Scabies
- HIV-associated dermatitis

Malignancy
- Cutaneous T cell lymphoma (mycosis fungoides/Sézary syndrome)

Immunodeficiencies
- Wiskott-Aldrich syndrome
- SCID
- Hyper-IgE syndrome
- IPEX (Immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome

Metabolic disorders
- Zinc deficiency
- Pyridoxine (vitamin B_6) and niacin deficiency
- Multiple carboxylase deficiency
- Phenylketonuria

Proliferative disorder
- Letterer-Siwe disease

Mycosis fungoides

- The most common form of CTCL
- Epidermotropic neoplasm of CD4+ T cells
- Need to consider in the differential diagnosis of any adult with eczematous rash without history of childhood AD

Dermatologic and immunologic findings in the immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome

- Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare genodermatosis associated with dermatitis, enteropathy, type 1 diabetes, thyroiditis, hemolytic anemia, and thrombocytopenia
- IPEX results from mutations of FOXP3, a gene located on the X chromosome that encodes a DNA-binding protein required for development of regulatory T cells
- Cutaneous findings may include dermatitis, bullae, urticaria, alopecia universalis, and trachyonychi
- Histopathologic examination of an active skin lesion revealed psoriasiform dermatitis

Nieves DS, et al. Arch Dermatol 2004;140:466

Major clinical features of AD

- Pruritus
- Chronic or relapsing course
- Typical distribution of dermatitis:
  - Facial and extensor involvement in children < 2 years old
  - Flexural involvement in children >2 years old or adults
- Personal or family history of atopy

Complicating features of AD

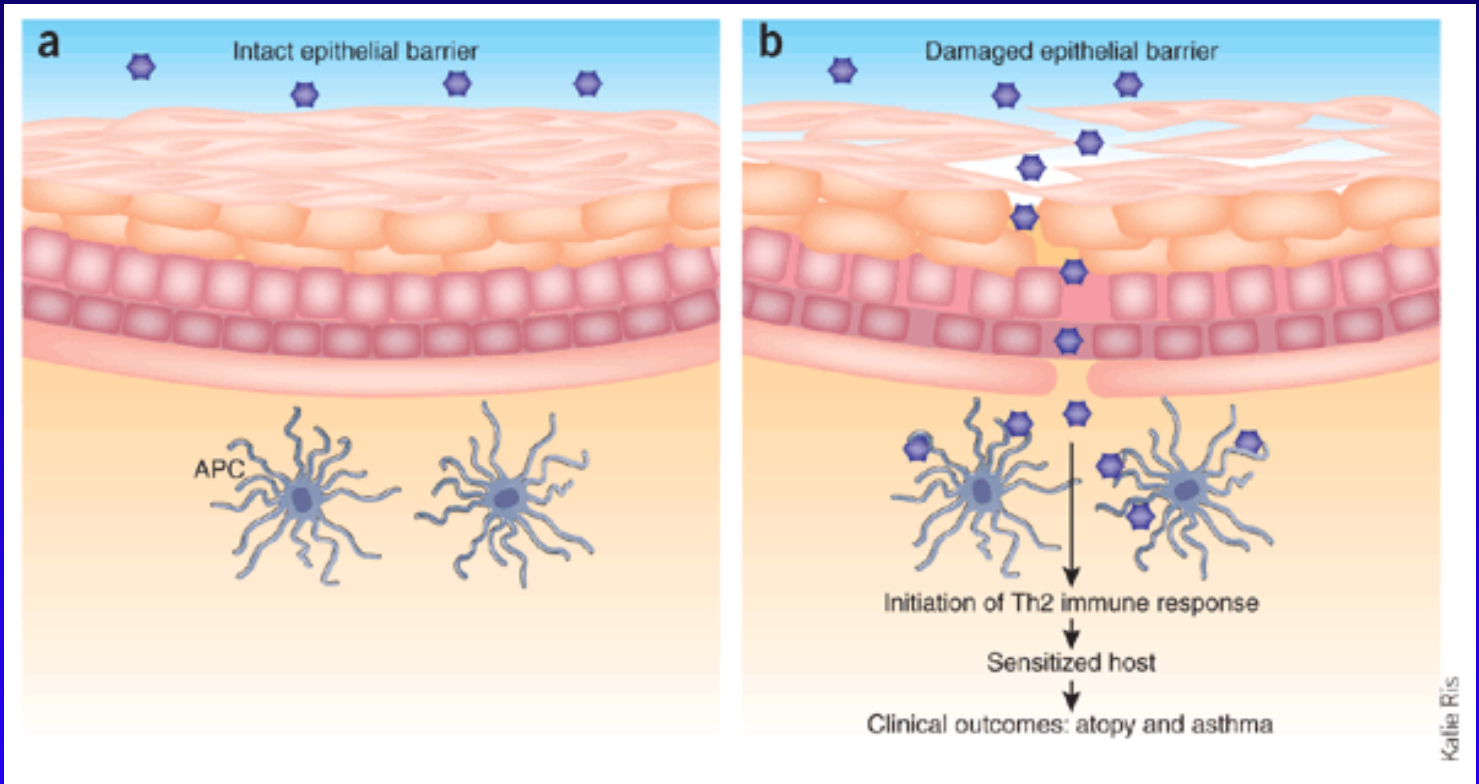
- Increased susceptibility to infections or colonization with a variety of organisms: *Staphylococcus aureus*, *Herpes simplex, Molluscum contagiosum, Malassezia furfur* (*Pityrosporum ovale*)
- Atopic keratoconjunctivitis presents with bilateral intense ocular pruritus, burning, tearing and copious mucoid discharge and may result in visual impairment from corneal scarring
- Non-specific hand dermatitis aggravated by repeated wetting, especially in the work environment leading to occupational disability

Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for AD

- Filaggrin is a key protein that facilitates terminal differentiation of the epidermis and formation of the skin barrier
- 2 loss-of-function genetic variants (R510X and 2282del4) in the gene encoding filaggrin (FLG) shown to be strongly associated with AD
- These variants also show highly significant association with asthma occurring in the context of AD
- This data suggests a key role for impaired skin barrier function in development of atopic disease

Palmer CNA, et al. Nature Genetics 2006;38:441

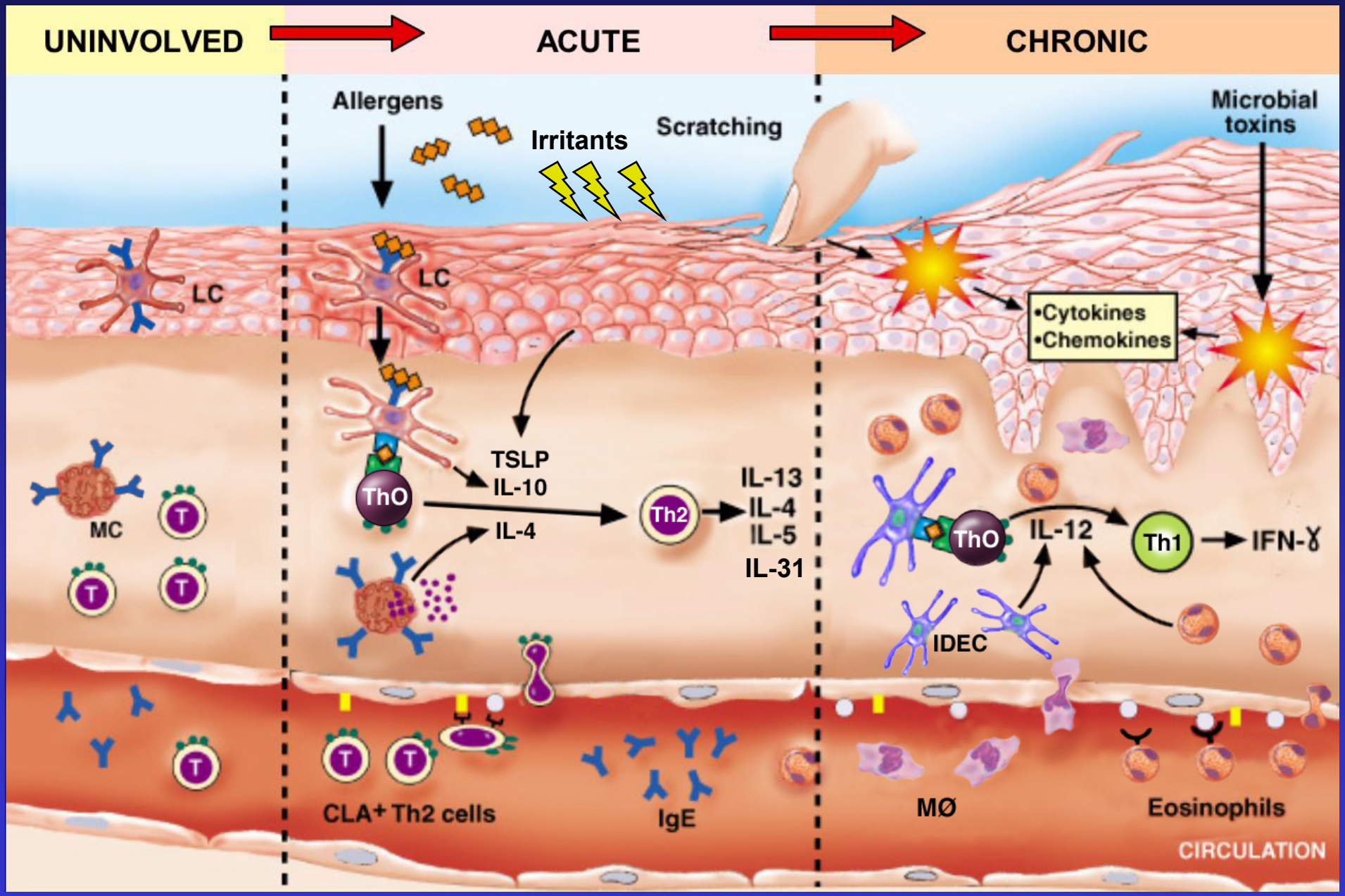
Skin barrier function and allergic risk



Hudson TJ. Nature Genetics 2006;38:399

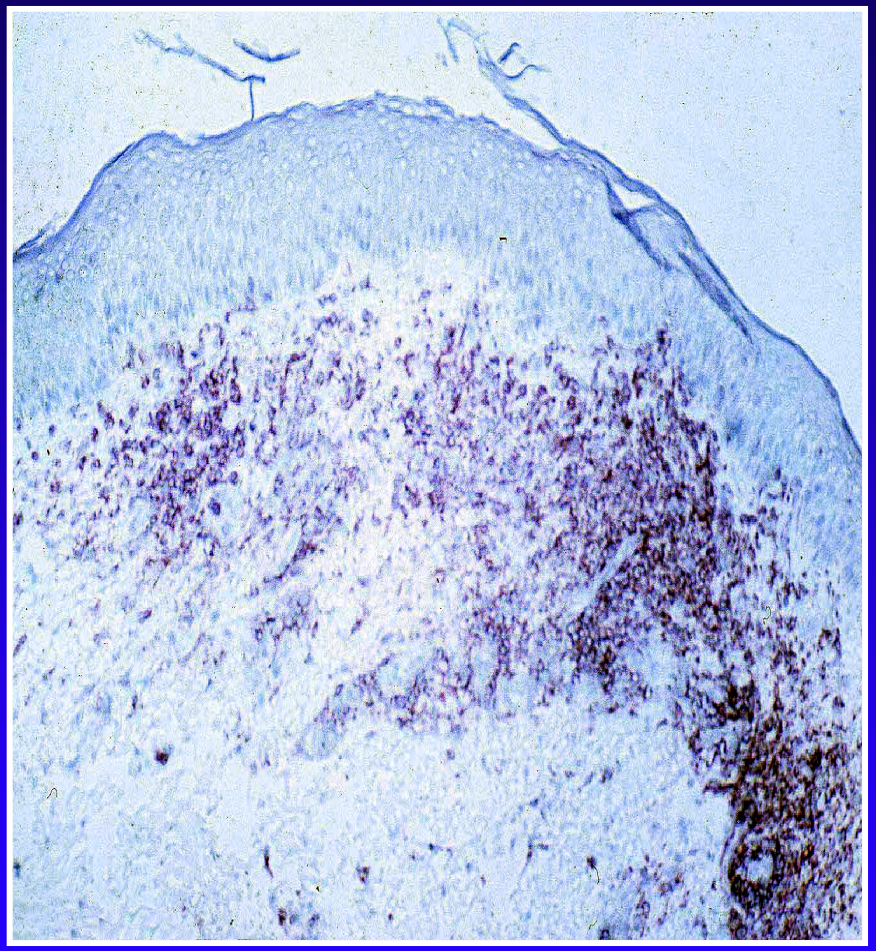
Systemic immune dysregulation in AD

- Increase IL-4, IL-5, IL-13 Th2 cells
- Decrease IFN-γ Th1 cells
- Increase CD86 on B cells
- Increase CD23 on PBMCs
- Increase serum IgE levels
- Increase eosinophils, ECP and MBP
- Increase CLA+ T cells
- Persistent monocyte activation with increased secretion of GM-CSF, PGE_2 and IL-10
- Increase spontaneous basophil histamine release



Leung DY, Boguniewicz M, et al. J Clin Invest 2004

T cells in AD skin



- Predominantly CD3, CD4 and CD45RO memory T cells that also express CD25 and HLA-DR on their surface, indicating intralesional activation
- Most T cells infiltrating into atopic skin lesions express high levels of the homing receptor cutaneous lymphocyte-associated antigen (CLA), a ligand for the vascular adhesion molecule, E-selectin

Cytokines in acute vs chronic AD lesions

- Acute inflammation is associated with predominantly IL-4 expression, whereas chronic inflammation is associated with IL-5 expression and eosinophil infiltration
- IL-13 expression higher in acute lesions, while chronic lesions have greater numbers of IL-12 mRNA-positive cells
- Decreased levels of IL-15 may contribute to both acute inflammation and elevated serum IgE
- Increased IFN-γ expression reported in chronic AD

Thymic stromal lymphopoietin

- TSLP is expressed by keratinocytes in acute and chronic lesions of AD, TSLP receptor by monocytes and DCs
- TSLP can activate DCs and induce their production of the Th2 cell–attracting chemokines CCL17 and CCL22
- Naive CD4+ T cells can be primed directly by TSLP to undergo proliferation and differentiation into Th2 lymphocytes

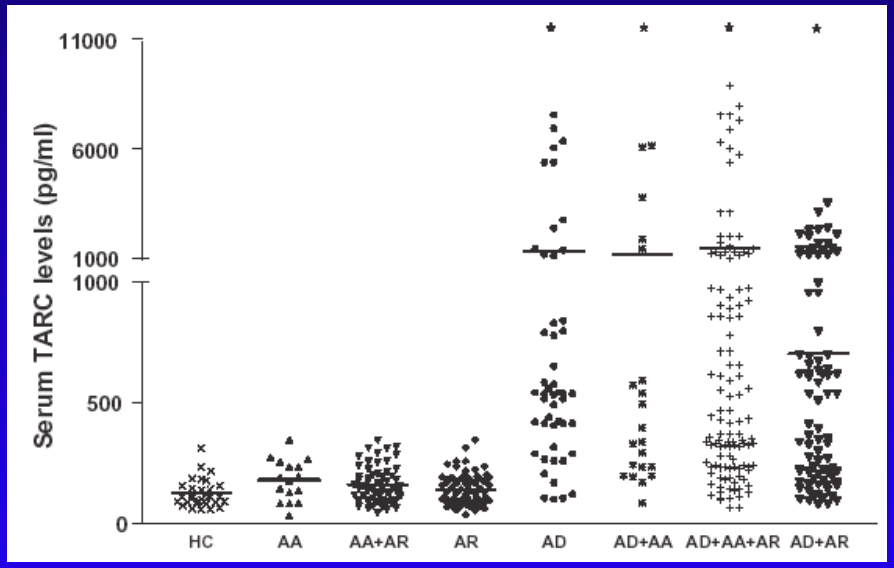
Interleukin-31

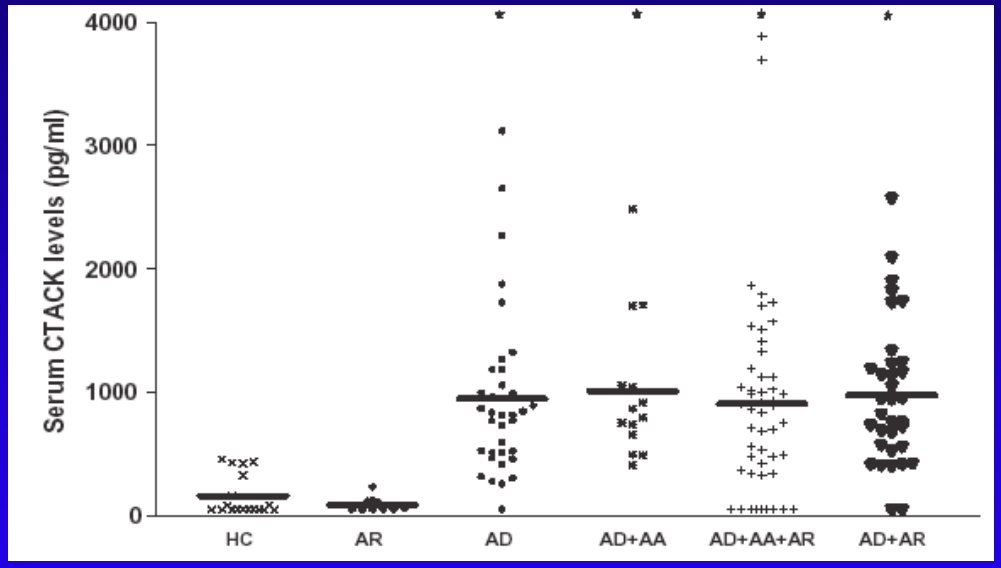
- IL-31 expression is associated with CLA+ T cells and might contribute to the development of AD-induced skin inflammation and pruritus

Chemokines in AD lesions

- Increased levels of IL-16, a potent chemoattractant for $CD4^+$ T cells seen in acute vs chronic lesions (Langerhans cells appear to primary source)
- C-C chemokines, RANTES, MCP-4, and eotaxin increased in AD lesions and likely contribute to the chemotaxis of eosinophils and T helper 2 cells into the skin
- Cutaneous T cell attracting chemokine (CTACK/CCL27), a chemokine produced primarily by keratinocytes has been shown to attract CLA+,CCR10+ T cells into the skin

Thymus and activation-regulated chemokine (TARC) & CTACK are disease-specific markers for AD

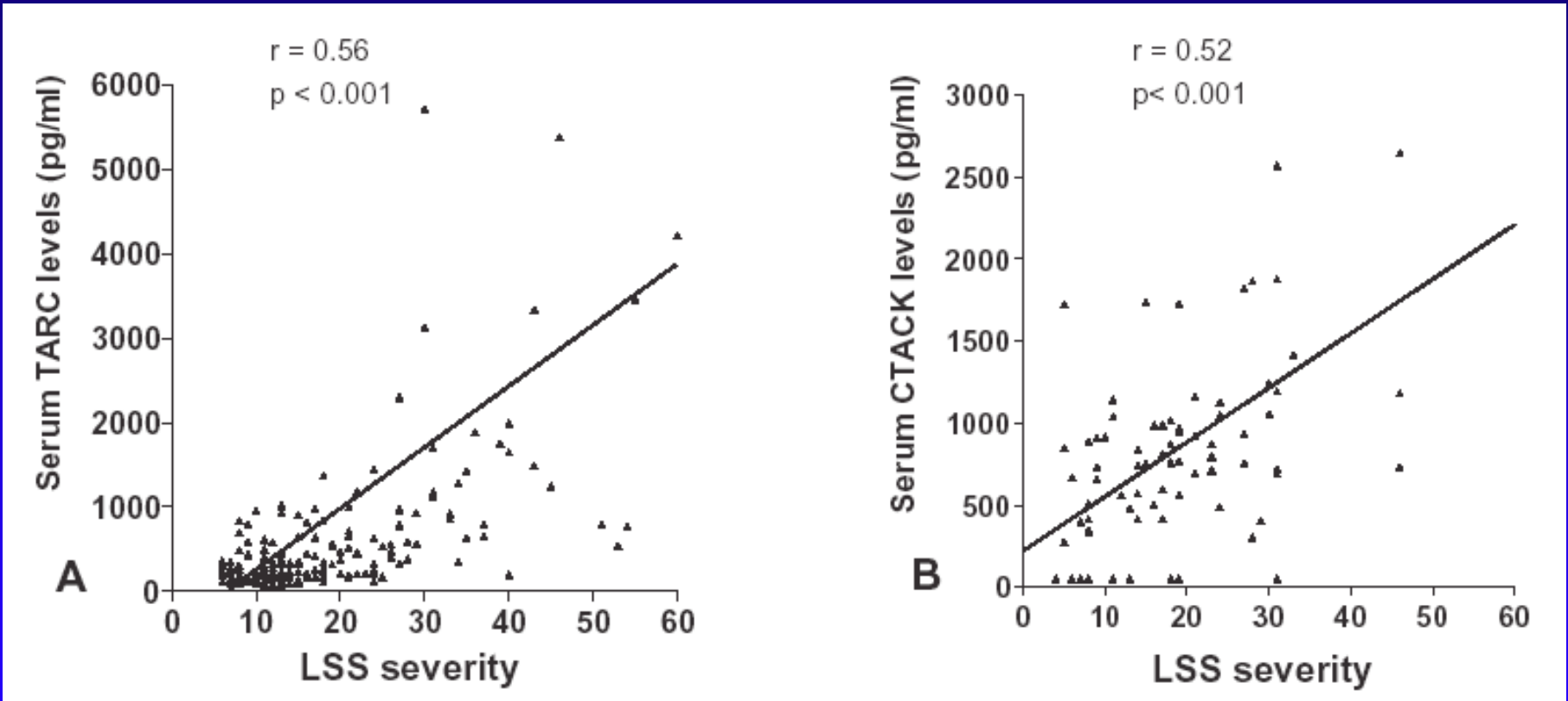




*P<0.05

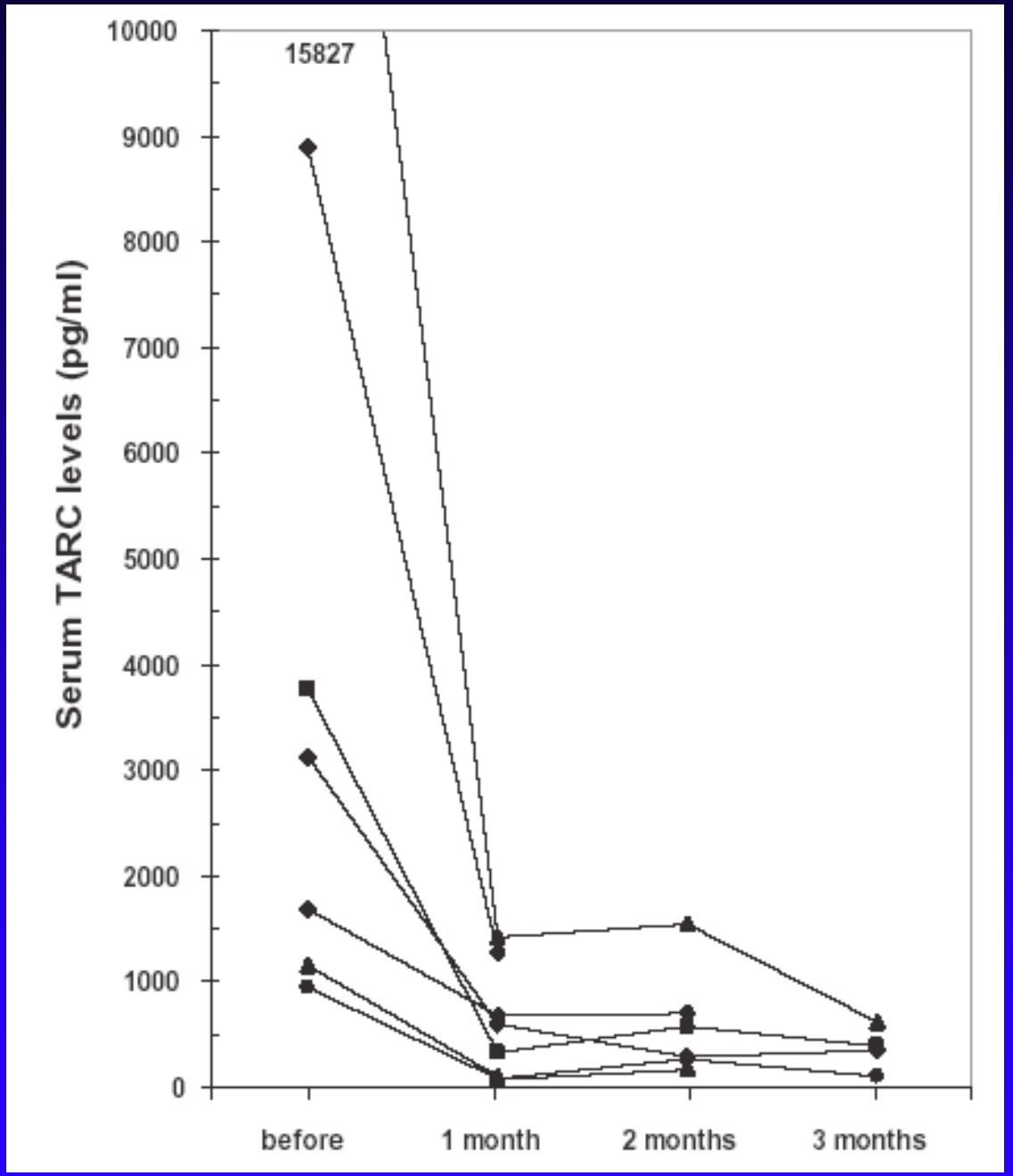
Hijnen DJ, et al. J Allergy Clin Immunol 2004;113:334

Serum TARC & CTACK levels correlate with disease activity in AD



Hijnen DJ, et al. J Allergy Clin Immunol 2004;113:334

Serum TARC levels decrease during treatment with CsA



Hijnen DJ, et al. J Allergy Clin Immunol 2004;113:334

T cell-mediated Fas-induced keratinocyte apoptosis plays a key pathogenetic role in AD

- Activated T cells induce keratinocyte apoptosis contributing to acantholysis (loss of intercellular adhesion) and spongiosis (intercellular edema) found in AD
- T cell-derived IFN-γ upregulates Fas on keratinocytes
- Lethal hit delivered by membranous and soluble Fas-ligand from CLA+ T cells

Langerhans cells in AD

- Langerhans cells (dendritic cells containing Birbeck granules) found in the epidermis and dermis express FcεRI that bind IgE
- Cell-bound IgE on Langerhans cells facilitates capture and internalization of allergens into Langerhans cells prior to their processing and antigen presentation to T cells
- FcεRI on Langerhans cells lacks the classic beta chain and its expression varies depending on the local inflammatory environment

Inflammatory dendritic epidermal cells

- Do not contain Birbeck granules
- Express higher levels of FcεRI vs Langerhans cells
- FcεRI activated IDECs prime naive T cells into IFN-γ– producing T cells and release IL-12 and IL-18, which together might lead to the switch of the initial TH2-type immune response into a TH1 type response

Eosinophils in AD lesions

- Activated eosinophils are present in significantly greater numbers in chronic as compared to acute lesions
- Deposition of eosinophil major basic protein can be detected throughout the upper dermis and to a lesser extent deeper in the dermis, especially in involved areas
- Serum levels of eosinophil cationic protein are elevated and correlate with disease severity

Immunologic triggers of atopic dermatitis

Role of food allergens

- DBPCFC have demonstrated that food allergens can cause exacerbations in a subset of patients with AD
- Seven foods (milk, egg, peanut, soy, wheat, fish and nuts) account for nearly 90% of positive challenges
- 1/3 of pediatric patients referred to a university dermatology practice for evaluation of eczema, rather than for suspected food allergy had IgE mediated food hypersensitivity

- Elimination of *relevant* food allergens results in improvement of skin disease and a decrease in spontaneous basophil histamine release
- Casein-reactive T cells from patients with milk-induced AD found to have significantly higher expression of CLA than *C. albicans*-reactive T cells from the same patients, and either casein- or *C. albicans*-reactive T cells from patients with milk-induced gastroenteropathy or normal controls

Role of aeroallergens

- Evidence supporting a role for aeroallergens in AD includes the finding of both allergen specific IgE antibodies and allergen specific T cells
- Both the respiratory route and direct contact with inhalant allergens may be important in the induction and exacerbation of AD
- Environmental control measures (dust mite avoidance) shown to result in clinical improvement of AD

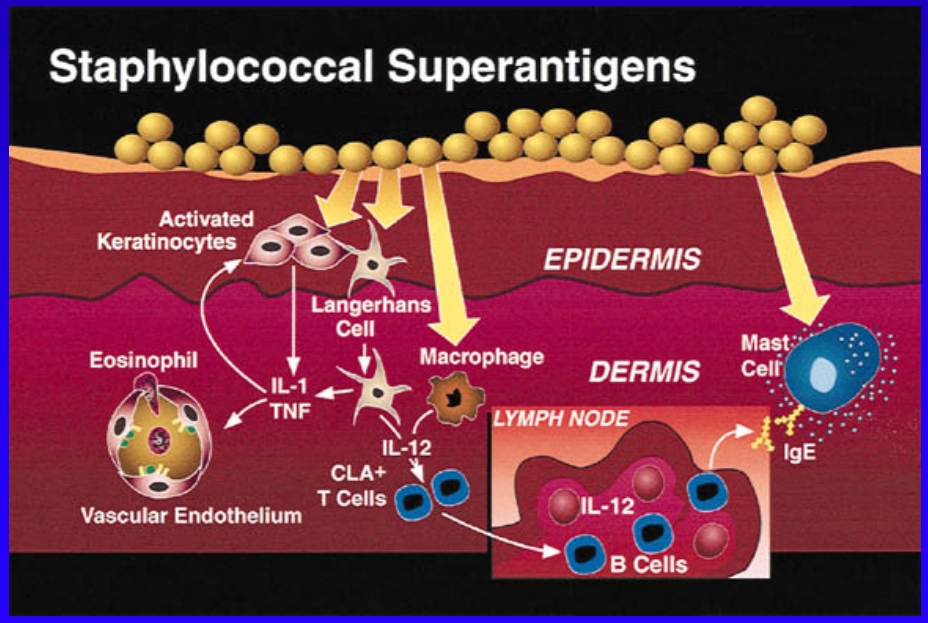
Role of autoantigens

- Sera from some patients with severe AD found to have IgE antibodies directed against human proteins
- Autoallergens have been cloned and found to be mainly intracellular proteins
- Release of these autoallergens from damaged tissues could trigger IgE- or T cell-mediated responses and maintain chronic allergic inflammation in severe AD

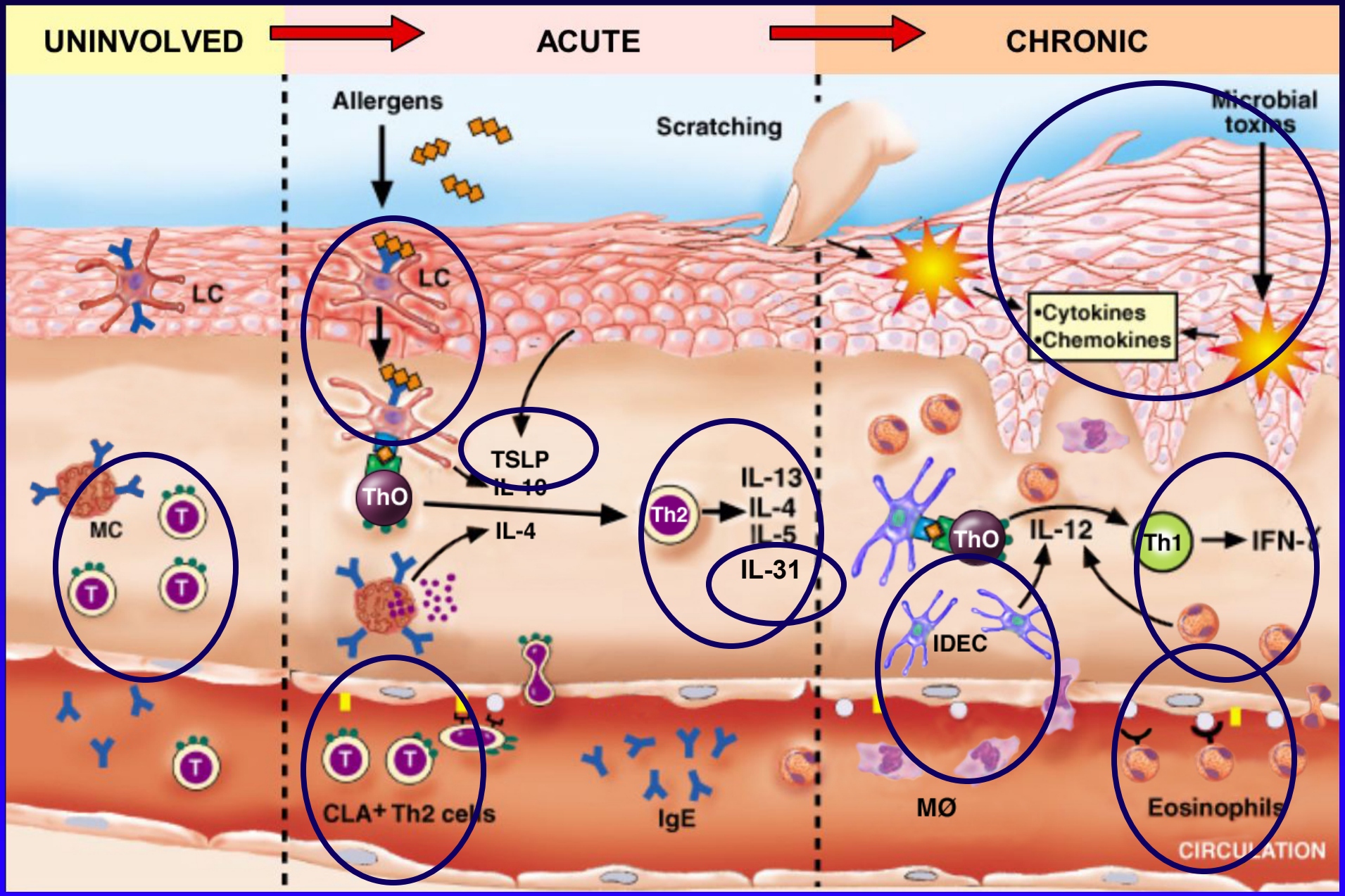
Role of microbial agents and toxins

- Patients with AD are colonized by high numbers of *S. aureus*, which can be cultured even from normal appearing skin
- Staph organisms may bind to proteins such as fibronectin and fibrinogen which are upregulated in inflamed skin
- Increased colonization may be associated with decreased secretion of antimicrobial peptides (e.g. HBD-2, LL-37) by keratinocytes, a defect in innate immunity mediated by IL-4 and IL-13

- Exotoxins secreted by *S. aureus* can act as superantigens contributing to persistent inflammation or exacerbations of AD
- >50% of AD patients studied have toxin producing *S. aureus* cultured from their skin



- AD patients can make specific IgE antibodies against the toxins on their skin and disease severity appears to correlate with the presence of these antibodies
- Basophils from patients with anti-toxin IgE release histamine on exposure to the relevant toxin, but not in response to toxins to which they have no specific IgE



Leung DY, Boguniewicz M, et al. J Clin Invest 2004

Antimicrobial peptides

- Diverse group of ~800 peptides derived from larger precursor molecules involved in innate immunity
- Widely distributed throughout plant and animal kingdoms suggesting fundamental role in evolution of multicellular organisms
- 2 major families of AMPs have been characterized in mammals: defensins and cathelicidins

Antimicrobial peptides

- As effectors of innate immunity, AMPs directly kill a broad spectrum of microbes, including gram-positive and gram-negative bacteria, fungi, and certain viruses

- Most AMPs maintain common structural features, including a cationic charge and the ability to interact with bacterial membranes through hydrophobic amino acids

AMP influence cellular immune responses

- Human cathelicidin LL-37
  - Chemoattractant binding to formyl peptide receptor-like 1
  - Chemotactic for mast cells
- Human β-defensins
  - Bind to CCR6 and are chemotactic for immature DC & memory T cells
  - HBD-2 promotes histamine release from MC

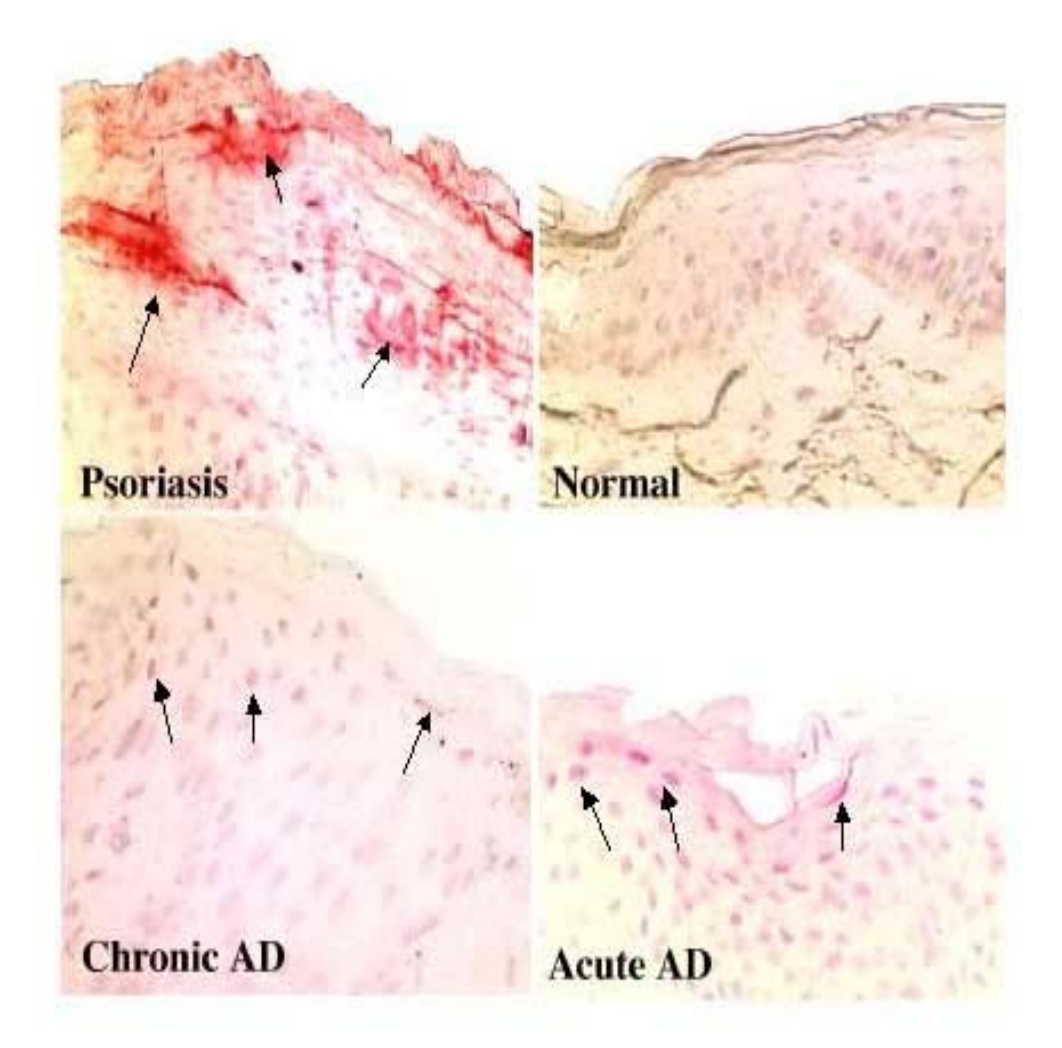
De Y, et al. J Exp Med 2000;192:1069
Niyonsaba F, et al. Immunology 2002;106:20
Yang D, et al. Science 1999;286:525
Befus AD, et al. J Immunol 1999;163:947

AMP and the skin

- Cathelicidin PR-39 first discovered in porcine wound fluid
- Human LL-37 observed in epidermal keratinocytes in inflammatory conditions such as psoriasis & increased post-injury
- HBD-2 and HBD-3 increased in lesional keratinocytes

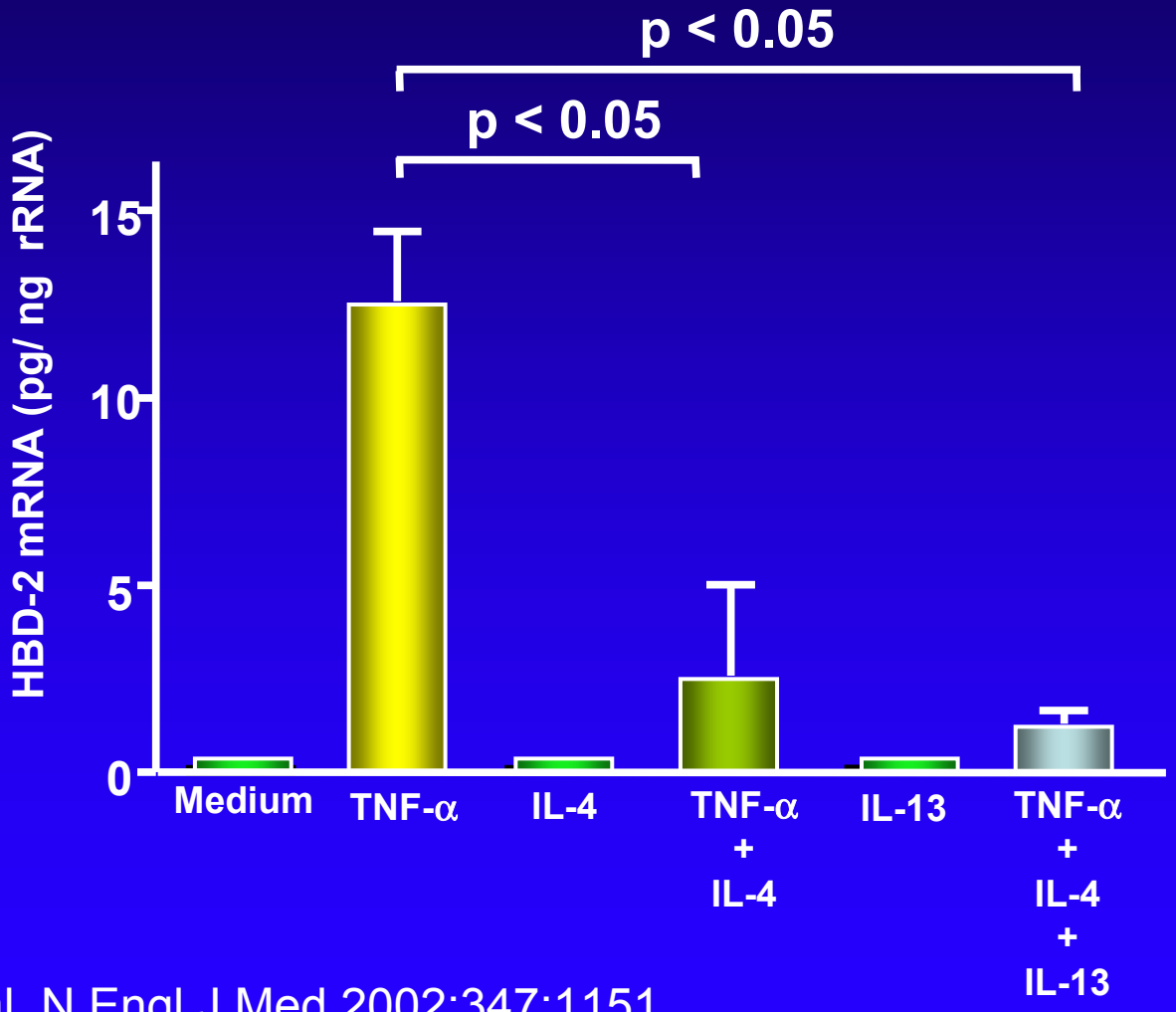
Gallo RL, et al. Proc Nat Acad Sci USA 1994;91:11035
Frohm M, et al. J Biol Chem1997;272:15258
Dorschner RA, et al. J Invest Dermatol 2001;117:91
Harder J, et al. Nature 1997;387:861

A deficiency in antimicrobial peptide (H-β-defensin-2) expression may allow *S. aureus* to colonize and infect skin of AD patients



Ong PY, et al. N Engl J Med 2002;347:1151

Effects of IL-4 and IL-13 on TNF-α-induced H-β-defensin-2 expression in HaCat cells



Ong PY, et al. N Engl J Med 2002;347:1151

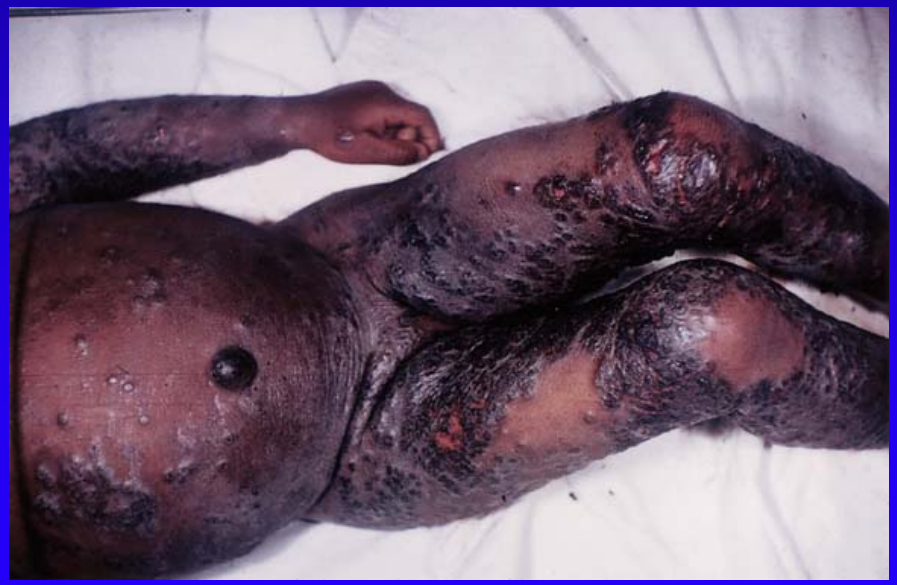
Suppression of innate immune response genes in AD

- Certain innate immune response genes are downregulated in AD skin compared with psoriasis
- HBD-3 showed lower expression in AD skin vs psoriasis
- Downregulation of a number of antimicrobial genes due to local upregulation of Th2 cytokines could explain the increased susceptibility of AD skin to bacterial, viral and fungal infections

Nomura, et al. J Immunol 2003;171:3262

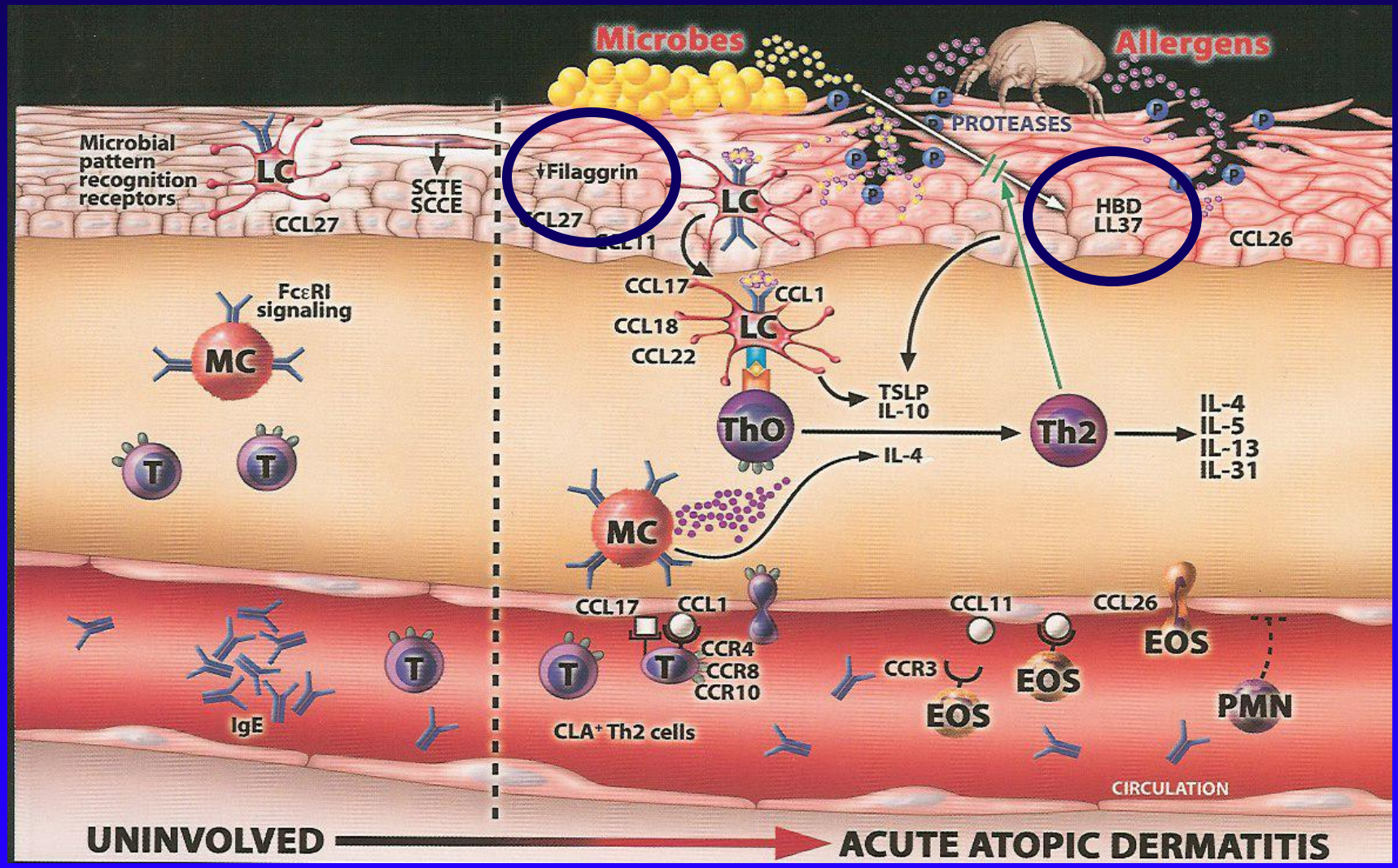
Eczema vaccinatum

- Even a past history of AD is considered a risk factor for eczema vaccinatum
- Deficiency of LL-37 in atopic skin may contribute to eczema vaccinatum



Engler R, et al. J Allergy Clin Immunol 2002;110:357

Howell MD, et al. J Immunol 2004;172:1763

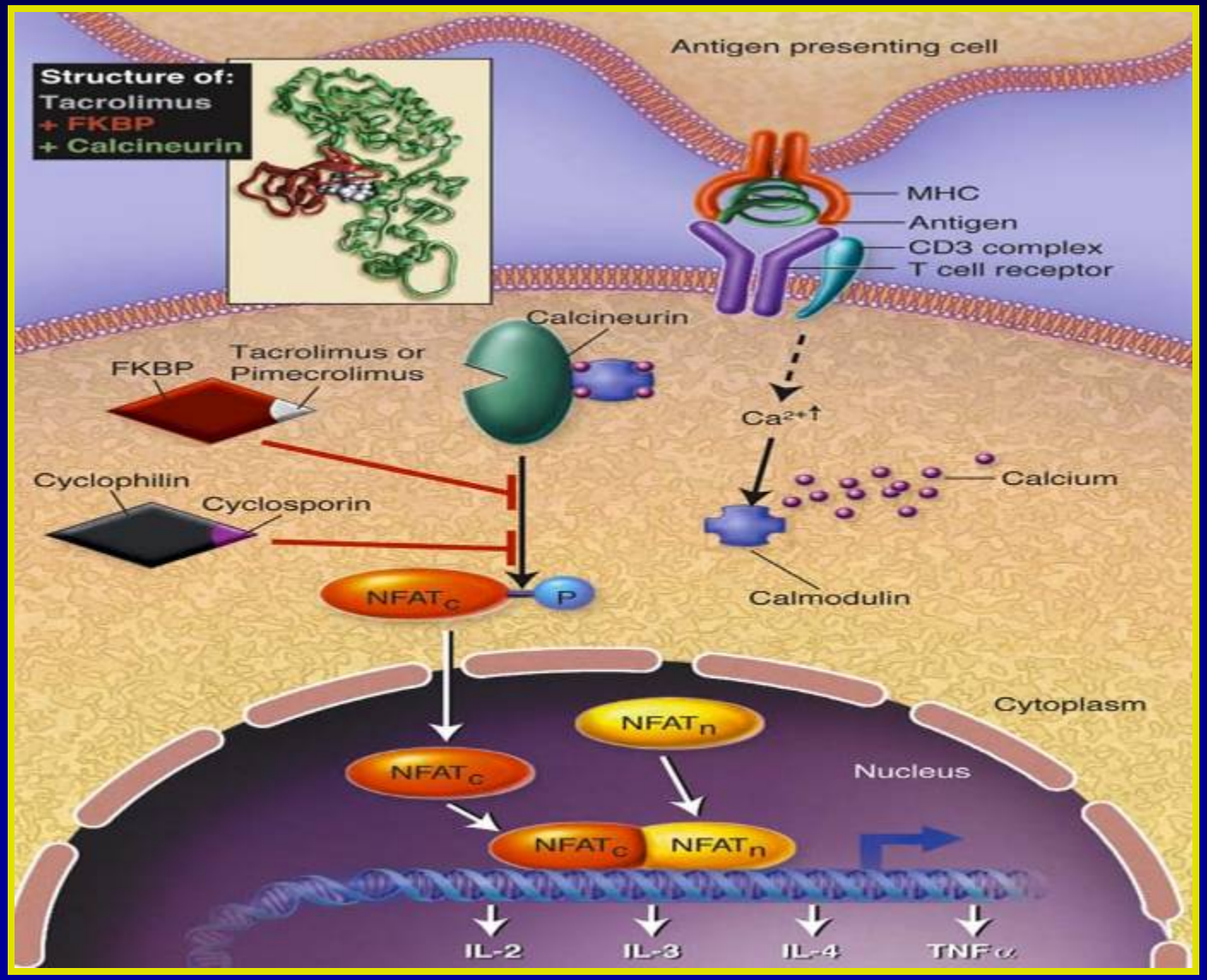


J Allergy Clin Immunol 2006;118

Topical calcineurin inhibitors

- Tacrolimus and pimecrolimus are non-steroidal macrolactones approx 800 Da in size
- Bind to intracellular binding proteins (immunophilins)
- This complex blocks the dephosphorylation of NFATc by the phosphatase portion of the calcineurin enzyme, thus interfering with transcription of Th1 and Th2-type cytokines
- Other cells (mast cells, dendritic cells) may also be targets for calcineurin inhibitors
- Chronic use not associated with skin atrophy

Calcineurin inhibitor activity



Nghiem, et al. J Am Acad Dermatol 2002